

REMARKS

Rejections Withdrawn

The Office communication mailed May 21, 2010 withdrew the following previously entered rejections:

1. alleged double patenting over co-pending application 11/510,280;
2. alleged double patenting over co-pending application 11/510,498;
3. alleged double patenting over co-pending application 11/512,725;
4. alleged double patenting over co-pending application 11/512,730;
5. alleged double patenting over co-pending application 11/512,735;
6. alleged double patenting over US Patent No. 7,098,190;
7. claims 73-78, 80, 81 and 98-101 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US 2007/0060538;
8. claims 73-78, 80, 81 and 98-101 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US 2008/0221051;
9. claims 69-81 and 98-100 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US 2008/0249041;
10. claims 69-81 and 98-100 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US 2007/0072819;
11. claims 69-81 and 98-100 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US 2007/0072820;
12. claims 73-78, 80, 81 and 98-101 under 35 USC 102(e) as allegedly anticipated by Becker *et al.* US Patent No. 7,098,190;

13. claims 77, 78, 80, 81 and 98 under 35 USC 102(b) as allegedly anticipated by Qui *et al.* (Current Biology Vol. 13:1697-1703, 2003);
14. claims 81-83 and 86-101 on an assertion of obviousness under 35 USC 103 over Becker *et al.* US Patent No. 7,098,190, Becker *et al.* US 2008/0221051, Becker *et al.* US 2008/0249041, Becker *et al.* US 2007/0072819, Becker *et al.* US 2007/0072820, Becker *et al.* US 2007/0060538 and Qui *et al.* (Current Biology Vol. 13:1697-1703, 2003).

New Rejection

The Examiner entered a single new rejection of all pending claims 102-121 under 35 USC 103 as allegedly obvious over (1) Becker *et al.* US 2008/0249041, (2) Becker *et al.* US 2007/0072819, (3) Becker *et al.* US 2007/0072820, in view of (4) Traub *et al.* (Exp. Eye Res. Vol. 73:291-302, 2001) and (5) Qui *et al.* (Current Biology Vol. 13:1697-1703, 2003).

All of Becker *et al.* US 2008/0249041, Becker *et al.* US 2007/0072819 and Becker *et al.* US 2007/0072820 relate in part to methods of promoting wound healing in a patient which comprises the step of administering a formulation comprising an antisense polynucleotide to a connexin protein, preferably connexin 43. Additionally,

- Becker *et al.* US 2008/0249041 discloses and claims a method of treating a subject having a wound, comprising administering to the wound an amount of a connexin 31.1 antisense polynucleotide effective to promote wound healing.
- Becker *et al.* US 2007/0072819 discloses and claims a method of treating a subject having a wound, comprising administering to the wound an amount of a connexin 32 antisense polynucleotide effective to promote wound healing.

- Becker et al. US 2007/0072820 discloses and claims a method of treating a subject having a wound, comprising administering to the wound an amount of a connexin 26 antisense polynucleotide effective to promote wound healing.

Traub et al. (Exp. Eye Res. Vol. 73:291-302, 2001) investigated corneal wound repair in rabbits following excimer laser ablation. In the healing process particular attention was focused on the epithelium and the authors reported the presence of both connexin 26 and connexin 43. Connexin43 was found also in corneal keratocytes and endothelial cells. According to the publication, both connexins were expressed throughout the corneal epithelium including migrating cells during regeneration. They also reported transient up-regulation 24 hours after wounding in the form of overlapping relocation to the upper cell layers. In the Abstract the authors concluded that transient “up-regulation and relocation of connexins within the regenerating epithelium may reflect the involvement of direct cell-cell communication in corneal wound healing” (emphasis added).

By contrast, Qui et al. (Current Biology Vol. 13:1697-1703, 2003) refers to the fact that connexin 43 is naturally down-regulated in the cells of the leading edge of skin wounds (see page 1702). The authors reported a series of experiments showing that a single topical application of a connexin 43 antisense gel in skin incisional and excisional mouse wound healing models brought about a transient down-regulation of connexin 43 protein levels, resulting in an increase in the rate of wound closure. The basis for this is found at page 1702, where the authors state that treatment with connexin 43 antisense appears to “kick-start the early stages of epidermal closure.” It was also reported to reduce inflammation in these models and to lead to a reduction in the extent of granulation tissue deposition and the subsequent formation of a smaller, less distorted, scar. In the final sentence of the Abstract, the authors conclude that, “This approach is

likely to have widespread therapeutic applications in other injured tissues and opens up new avenues of research into improving the wound healing process.”

The basis for the Examiner’s rejection is summarized at page 11 of the May 21, 2010 Office communication, where he states that the art teaches “that down regulation of connexin proteins in wound promotes wound healing.” The Examiner notes in particular antisense to connexin 43. Although acknowledging that none of the cited art refers to the treatment of eye wounds with connexin 43 antisense, the Examiner states that the art has “[1] shown that connexin 43 is correlated with eye wounding and furthermore has [2] shown that the action of connexin 43 in eye wound is similar to the action of connexin 43 in other tissues.” Applicants traverse this rejection.

Qui *et al.*, which was co-authored by Applicants Becker and Green, supports the idea that connexin 43 down-regulation (in that case with antisense polynucleotide) enhanced incisional and excisional wound-healing. Traub *et al.*, on the other hand, report on the status of connexin 43 and 26 following a laser ablation wound to the cornea of the eye, and states that, “During regeneration following laser ablation both [connexins] were expressed throughout the epithelium including the migrating cells” and both were “slightly up-regulated...” (page 301; emphasis added). Traub *et al.* conclude that these findings “suggest [the] involvement [of connexins 43 and 26] in the regulation of epithelial wound healing.” This is discussed in further detail at pages 300-301 of Traub *et al.*, where the authors state, for example, that “we detected Cx 43 and Cx26 throughout the healing corneal epithelium” and that “wounding caused up-regulation and rearrangement of both [connexins] around the original wound edge including the limbal areas.” They further conclude at page 300 that, “These and other results showing dynamic modulation of gap junction expression accompanying epithelial proliferation and differentiation may reflect the

regulatory role of direct cell-cell communication in the coordinated rebuilding of stratified epithelia” (page 300, col. 1; emphasis added).

Thus, given that Traub *et al.* refers to the requirement for connexin 43 up-regulation in the corneal epithelium following an eye wound, and a possible regulatory role for direct gap junctional cell-cell communication in the healing of eye wounds, it plainly teaches away from the use of an agent, including antisense, to down-regulate connexin 43 to enhance healing. As such, and in contrast to the conclusion in the May 21, 2010 Office communication that one would be motivated by the cited art “to treat eye wounds with antisense compounds targeting connexin 43,” Applicants submit that the opposite is true. Additionally, Applicants note that the Becker *et al.* patent application documents cited by the Examiner regarding down-regulation of connexins (including connexin 43) with antisense for wound healing was first filed on January 27, 2000 and claims the benefit of priority to NZ 333928 (filed January 27, 1999) and NZ 500190 (filed October 7, 1999). Traub *et al.* was co-authored by Applicant Becker and published based on a revised manuscript submitted on April 11, 2001 – well over a year later – yet it makes no mention of the use of any agent, including connexin 43 antisense, to enhance the healing of an eye wound.

Applicants respectfully request that the Examiner reconsider and withdraw his rejection, and reconsideration and allowance of all presently pending claims is respectfully requested.

The Commissioner is hereby authorized to charge the requisite fees, or any fees in connection with this application during its entire pendency, or to credit any overpayment, to Deposit Account No. 04-1679.

Respectfully submitted,

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